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The biosimilar road in inflammatory bowel disease: The right way?

Gionata Fiorino, MD, PhD, Consultant [1],
Silvio Danese, MD, PhD, Head of IBD Center *

IBD Center, Department of Gastroenterology, Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy

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A B S T R A C T

The biologicals have led to dramatic changes in the management of immune-mediated diseases, and the subsequent development of their biosimilars may reduce the high costs of these agents. However, there remain concerns about the true equivalence of a biosimilar and its reference product, as well as around immunogenicity of these agents in IBD, although studies on rheumatoid arthritis support the similarity of biosimilars and their originators. Many of the biologicals are approved for multiple indications, but it is not always possible to extrapolate across indications for the corresponding biosimilars. For both reference agents and biosimilars, rare adverse events and long-term efficacy and safety can only be assessed through post marketing surveillance; therefore, particular emphasis should be placed on the traceability of these agents in clinical practice. Lastly, based on current data, biosimilars cannot be considered simple substitutes of reference products in IBD, unless demonstrated by well-designed randomized controlled trials.

Introduction

The introduction of monoclonal antibodies, termed biologicals, led to dramatic changes in the management of, as well as the course of, immune-mediated diseases, such as rheumatoid arthritis,

* Corresponding author. Tel.: +39 0282244771; fax: +39 0282242591.
E-mail addresses: gionataf@gmail.com (G. Fiorino), sdanese@hotmail.com (S. Danese).
[1] Tel.: +39 0282247225; fax: +39 0282242591.

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ankylosing spondylitis, psoriasis, ulcerative colitis (UC) and Crohn's disease (CD) [1–3]. In particular, the use of anti-tumour necrosis factor (TNF) agents, such as infliximab, etanercept, adalimumab, certolizumab, and golimumab, as well as new molecules, such as ustekinumab, an anti-IL-12/23 monoclonal antibody, have modified progression of the above chronic conditions, by preventing structural damage progression, thus resulting in reduced need for surgery and hospitalization [4]. In addition, prolonged maintenance therapy with anti TNF agents has been shown to reduce the occurrence of severe complications and to improve quality of life.

The main limitation associated with the biologicals is their high cost [5]. The biologicals are large and very complex molecules, approximately 1000 times the size of chemically synthesized drugs, that are produced by living cell cultures, thus requiring significant investment. While available data support the cost effectiveness of the biologicals [6], largely due to better disease control, use of these agents can be very expensive in the long term [5,7], placing a significant burden on National Healthcare Systems. In an era where cost reduction is of utmost importance, this limitation is significant, and may limit the use of these highly effective agents.

Biosimilars

The European Medical Agency (EMA) defines a biosimilar as a biological medicinal product that is similar to a biological medicine that has already been authorized, the so-called 'reference medicinal product'. The reference product is defined as a medicinal product that has been granted a marketing authorization by a Member State or by the European Commission on the basis of a complete dossier [8]. The concomitant expiration of patents on some biologicals such as infliximab and the development of their biosimilars raised the issue of using biosimilars to reduce costs associated with the treatment of chronic inflammatory diseases. However, the expected cost saving is unlikely to be of the same magnitude seen with generic versions of chemical medicines.

For a biosimilar to be approved for the same indications as the originator, there are a number of conditions that must be met. Both medications must be comparable in terms of efficacy and safety, have similar immunogenicity, be effective for all approved indications, and interchangeable for the same indication. Traceability is also required, in order to identify particular safety aspects, which can be different even for the same molecule overtime. Some concerns have been raised regarding these aspects in recent months, following the decision to approve two infliximab biosimilars, which may be prescribed as soon as the patent for the originator expires in Europe.

In this review, we aim to explore some of the most important aspects of the biosimilars and biosimilarity, focusing on the role of biosimilars in inflammatory bowel disease (IBD).

Comparability

A biosimilar and its reference product are expected to have the same safety and efficacy profile, and are generally used to treat the same conditions. However, there remain some concerns regarding the true equivalence of biosimilars and originators (reference products). Due to the complexities of manufacturing copies of biological therapeutics, biosimilars may or may not have differing biological function, efficacy or toxicity from the reference products. Even minor modifications in manufacturing processes may alter biological functions and/or immunogenicity, potentially changing safety and efficacy profiles. Thus, the key question for biosimilars is not whether differences exist compared with the reference products, but whether such differences are clinically relevant.

Between 2003 and 2005, the EMA addressed the challenge of determining comparability by establishing that the development of biosimilars should satisfy the 'comparability exercise'. This entails a stepwise head-to-head comparison of quality, safety and efficacy in order to demonstrate that a biosimilar and its reference medicinal product are similar in these areas. Even if present, disparities may not be revealed in limited sample size clinical studies, due to the minimal heterogeneity that may arise with changes in manufacturing processes [9–12]. Therefore, in 2012, the European Commission changed its position on the use of the reference medicinal product in the comparability exercise [13]. Previous requirements of an exclusive use of products licensed in the European Economic Area (EEA) were changed in accepting critical data for comparisons from reference products authorized in